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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,786	11/08/2000	Sudhir Agrawal	47508.700	2469

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/708,786	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-15,17-24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-15, 17-24, 26, and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 5, 2004 has been entered.

Claims 7, 16, and 25 have been canceled. Claims 3, 6, 9, 15, 18, 24, and 27 have been amended.

Claims 1-6, 8-15, 17-24, 26, and 27 have been examined on the merits.

Response to Amendment

Applicants Amendment and Response filed March 5, 2004, has been considered. Rejections and/or objections not reiterated from the previous office action mailed November 5, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Specification

The use of the trademark CAMPOTOSAR® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Claim 10 is objected to because of the following informalities: Claim 10 contains the word "the" twice in line 3. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8-15, 17-24, 26, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6, 8-15, 17-24, 26, and 27 recite the limitation, "statistically significantly potentiating the activity of a prodrug". It is unclear what is meant by "statistically significantly potentiating the activity of a prodrug". Without a specific definition of what is "statistically significant", one of ordinary skill in the art is not apprised of the metes and bounds of the claim. For example, by what statistical meter would such values be determined and what values would be deemed significant?

Response to Arguments

It is noted that a similar rejection was made of record in the Office Action filed on June 19, 2002. This rejection was subsequently withdrawn in the Office Action filed March 11, 2003, in view of Applicant's arguments. However, after careful reconsideration of the claims, it is determined that this rejection is warranted.

In response to the similar rejection made in the Office Action filed on June 19, 2002, Applicants argued that statistical significance was determined by employing an unpaired t-test. Applicants contend that exemplary p valued deemed to be statistically significant using this model fell in the range of $p<0.08$ to $p<0.0001$. Applicants argue that the specification provides adequate guidance for what values would be judged statistically significant, and what test was used to calculate those values.

Applicant's arguments have been reconsidered, but are not found persuasive because the term "statistically significant" has not been defined by the instant specification. Although an unpaired t-test was used to determine statistical significance in, for example, Example 1, this test nor its p values are required by the instant claims. Therefore, one of ordinary skill in the art is not apprised of the metes and bounds of the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8-15, 17-24, 26, and 27 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a method for statistically potentiating the

activity of CAMPOTOSAR® (irinotecan), the method comprising co-administering an oligonucleotide with CAMPOTOSAR®, wherein the oligonucleotide does not have two 5' and four 3' 2-0-methyribonucleosides, and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1, does not reasonably provide enablement for a method for statistically significantly potentiating the activity of a prodrug, the method comprising co-administering an oligonucleotide with the prodrug, wherein the oligonucleotide does not have two 5' and four 3' 2-0-methyribonucleosides, and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary.

Claims 1-6, 8-15, 17-24, 26, and 27 are broadly drawn to a method for statistically significantly potentiating the activity of any prodrug, the method comprising co-administering an oligonucleotide with the prodrug, wherein the oligonucleotide does not have two 5' and four 3' 2-0-methyribonucleosides, and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1.

The specification provides examples for a method for statistically potentiating the activity of CAMPOTOSAR® (irinotecan), the method comprising co-administering mdm-2 or HIV-1

specific oligonucleotides represented by SEQ ID NO:1 or SEQ ID NO:2, respectively. The specification also provides an example for a method for statistically potentiating the activity of CAMPOTOSAR®, the method comprising co-administering an arbitrary oligonucleotide represented by SEQ ID NO:3. The art teaches a method for potentiating the activity of the prodrug, CAMPOTOSAR®, comprising co-administering a mismatch control oligonucleotide (see Wang et al., Clinical Cancer Research, 2001 Vol. 7:3613-3624). The art also teaches a method for potentiating the activity of the prodrug, CAMPOTOSAR®, comprising co-administering two protein kinase RI α subunit specific oligonucleotides (see Agrawal et al., International Journal of Oncology, 2001 Vol. 18:1061-1069). There are no examples provided in the instant specification for a method for statistically significantly potentiating the activity of any prodrug, other than CAMPOTOSAR® comprising co-administering an oligonucleotide.

At the time the instant invention was made, the empirical phenomenon of synergy was unpredictable. Merriam-Webster Online Dictionary, 2004, defines the term, "potentiate" as "to augment the activity of (as a drug) synergistically" (see attached definition by Merriam-Webster Online Dictionary). Therefore, given their broadest reasonable interpretation, the claims encompass combination therapy wherein synergy, as opposed to additive effects are desired. It is well known in the art that synergistic events are wholly unpredictable and wildly vulnerable to chance.

Further, the claimed methods read on a method for statistically significantly potentiating the activity of any prodrug, where, it has been shown that potentiation of, for example, the prodrug CAMPOTOSAR® (irinotecan), by oligonucleotides is unique for irinotecan or perhaps the class of prodrugs (see Agrawal et al. International Journal of Oncology, 2001 Vol. 18:1061-

1069, specifically at page 1068, last paragraph). Agrawal et al. further teach that potentiation of irinotecan by oligonucleotides is dependent on many factors including the dose of irinotecan, the dose of the oligonucleotide, the type of modification of the oligonucleotide, the duration of oligonucleotide treatment, and the metabolic stability of the oligonucleotide (see for example, Figure 3A, page 1065, first and second columns and page 1068, last paragraph). The teachings of Agrawal et al. suggest an unpredictable nature, requiring many factors, regarding the synergy between oligonucleotides and irinotecan.

This unpredictable nature is further supported by Wang et al. (Clinical Cancer Research, 2001 Vol. 7:3613-3624) who found that, to their surprise [emphasis added], a mismatch control oligonucleotide potentiated the efficacy of irinotecan (see Figure 3C). Wang et al. suggest that these results indicate a unique interaction between oligonucleotides and irinotecan.

The specification as filed, and the art, provide methods for statistically potentiating the activity of the prodrug CAMPOTOSAR®, the method comprising co-administering an oligonucleotide. The specification and the art do not teach any other prodrug other than CAMPOTOSAR®. The phenomenon of synergy is an unpredictable one, and the art of statistically potentiating the activity of the prodrug CAMPOTOSAR® is unpredictable as discussed in the teachings of Agrawal et al. and Wang et al. Due to the unpredictability in the art, one skilled in the art would need to practice undue trial and error experimentation to practice the instant invention over the scope claimed. The skilled artisan would need to first determine the dose of the prodrug, the dose of the oligonucleotide, the type of modification of the oligonucleotide, the duration of oligonucleotide treatment, and the metabolic stability of the

oligonucleotide, to practice the methods as claimed. These factors are not routine and the skilled artisan would need to determine such factors de novo, through empirical, undue experimentation.

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of specific guidance by the inventor, the lack of working examples, and the quantity of experimentation that would be required, it would require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed, over the full scope claimed.

Response to Arguments

It is noted that a similar rejection was maintained in the previous Office Action, filed November 5, 2003. In response to this similar rejection, Applicants argued that the method of the invention utilizes oligonucleotides as a general class, and not of any particular sequence. Applicants argue that explicit disclosure of methods of making innumerable oligonucleotides not having the sequence of SEQ ID NO:1 are well known in the art, and would not require undue experimentation to make and use. Applicants contend that Example 1 demonstrates that both a mdm-2 specific and HIV specific oligonucleotide statistically potentiates Camptosar efficacy. Applicants argue that the potentiation occurs in a target sequence-independent manner. Applicants rely on Example 2, which teaches that an arbitrary sequence referred to as SEQ ID NO:3 statistically potentiates prodrug efficacy. Applicants further rely on two post filing references which teach a mismatch control oligonucleotide and two antisense oligonucleotides designed to target human protein kinase RI α subunit also have a prodrug potentiating effect.

Applicants also argue that Agrawal et al., a reference relied upon for enablement purposes in the previous Office Action, filed November 5, 2003, recites that "the potentiation of antitumor activity of irinotecan is dependent on the dose of irinotecan and chemically modified oligonucleotide, suggesting requirement of the presence of a certain level of irinotecan and oligonucleotide in the system". Applicants also point out that Agrawal et al. goes on to state that "a certain level of oligonucleotide in the system (is needed for prodrug potentiation)." Applicants note that the doses to be delivered in the method of the invention are directly supported in the examples in the specification.

Applicant's arguments have been fully considered. In light of Applicants arguments, the Examiner has reconstructed the 35 USC 112, first paragraph rejection in light of the specification and what is known in the art. The Examiner agrees that the specification as filed, combined with what is known in the art would lead the skilled artisan to believe that the potentiation occurs in a target sequence-independent manner. However, the specification, combined with what is known in the art do not teach the skilled artisan how to devise a method for statistically potentiating the activity of any prodrug, other than CAMPOTOSAR® (irinotecan) comprising the co-administration of oligonucleotides. The art suggests that the potentiation of the activity of CAMPOTOSAR® by oligonucleotides is unique and is an unexpected result. This fact is pointed out, several times, by Applicants arguments in which Applicants refer to specific factors and criteria which must be met to result in the potentiation of prodrug efficacy. In this regard, it would require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed, over the full scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 10-14, and 19-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Koike et al. (Cancer Research, 1997 Vol. 57:5475-5479).

Koike et al. teach a method for potentiating the activity of the prodrug, Camptosar (CPT-11) comprising administering an antisense oligonucleotide with the prodrug. Koike et al. teach an antisense cDNA enhances drug sensitivity in HepG2 cells treated with CPT-11. For example, Koike et al. teach HepG2 cells transfected with a cMOAT antisense cDNA are more sensitive to CPT-11 than cells not transfected with the antisense cDNA (see Table 1). It is noted that the active compound of CPT-11 is SN-38, as recited in claims 3, 4, 12, 13, 21, and 22.

Therefore, Koike et al. anticipate claims 1-5, 10-14, and 19-23.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8-15, 17-24, 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koike et al. (Cancer Research, 1997 Vol. 57:5475-5479) in view of Baracchini et al. [U.S. Patent No. 5,801,154].

Claim 1 is drawn to a method for statistically significantly potentiating the activity of a prodrug, the method comprising co-administering an oligonucleotide with the prodrug, wherein the oligonucleotide does not have two 5' and four 3' 2-0-methyribonucleosides, and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1. Claims 2-6, 8 and 9 are dependent on claim 1 and include the limitations of claim 1, with the further limitations wherein the prodrug is an active compound, wherein the anti-cancer drug is SN-38, wherein the prodrug is Camptosar and wherein the oligonucleotide comprises phosphorothioates, phosphorodithioates, and 2'-O-substituted ribonucleoside linkages. Claim 10 is drawn to a method for statistically significantly potentiating the activity of a prodrug, the method comprising co-administering an oligonucleotide with the prodrug, wherein the oligonucleotide is administered before the prodrug. Claims 11-15, 17, and 18 17-24, 26, and 27 are dependent on claim 10 and include the limitations of claim 1, with the further limitations wherein the prodrug is an active compound, wherein the anti-cancer drug is SN-38, wherein the prodrug is Camptosar and wherein the oligonucleotide comprises phosphorothioates, phosphorodithioates, and 2'-O-substituted ribonucleoside linkages. Claim 19 is drawn to a method for statistically significantly potentiating the activity of a prodrug, the method comprising co-administering an oligonucleotide with the prodrug, wherein the prodrug is present in an amount that would not be

therapeutically effective in the absence of the oligonucleotide. Claims 20-24, 26, and 27 are dependent on claim 19 and include the limitations of claim 1, with the further limitations wherein the prodrug is an active compound, wherein the anti-cancer drug is SN-38, wherein the prodrug is Camptosar and wherein the oligonucleotide comprises phosphorothioates, phosphorodithioates, and 2'-O-substituted ribonucleoside linkages.

Koike et al. teach a method for potentiating the activity of the prodrug, Camptosar (CPT-11) comprising administering an antisense oligonucleotide with the prodrug. Koike et al. teach an antisense cDNA enhances drug sensitivity in HepG2 cells treated with CPT-11. For example, Koike et al. teach HepG2 cells transfected with a cMOAT antisense cDNA are more sensitive to CPT-11 than cells not transfected with the antisense cDNA (see Table 1). It is noted that the active compound of CPT-11 is SN-38, as recited in claims 3, 4, 12, 13, 21, and 22. Koike et al. do not teach wherein the oligonucleotide comprises phosphorothioates, phosphorodithioates, and 2'-O-substituted ribonucleoside linkages.

Baracchini et al. teach phosphorothioate oligonucleotides with 2'-O-methylribonucleoside modifications at varying positions (see for example, columns 6-9). Baracchini et al. teach such modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases.

It would have been obvious to one of ordinary skill in the art to devise a method for potentiating the activity of the prodrug, Camptosar (CPT-11) comprising administering an antisense oligonucleotide with the prodrug as taught by Koike et al. It would have been further obvious to modify the oligonucleotides with modifications, including to 2'-O-substituted

modifications as taught by Baracchini et al. because such modifications were routine and well known in the art to enhance the stability, uptake and affinity of an antisense molecule. One of ordinary skill in the art would have been motivated to modify the oligonucleotide of the instant invention since the metabolic stability of the oligonucleotide plays an important factor in statistically potentiating CPT-11 prodrug efficacy, as evidenced by Agrawal et al. (International Journal of Oncology, 2001 Vol. 18:1061-1069).

Therefore, the invention of claims 1-6, 8-15, 17-24, 26, and 27 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
May 13, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER